Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding adviezen herevaluatie bestuurlijke MAC-waarden
Uw kenmerk : ARBO/AMIL/97/00648
Ons kenmerk : U 2706/CB/MP/563-O3
Bijlagen : 18
Datum : 14 december 2000

Mijnheer de staatssecretaris,

Op verzoek van uw ambtsvoorganger bied ik u hierbij de eerste adviezen aan van een reeks over de gezondheidskundige basis van uit het buitenland overgenomen grenswaarden voor beroepsmatige blootstelling aan stoffen. Het verzoek om deze adviezen is in algemene zin vervat in brief nr ARBO/AMIL/97/00648 en in latere stadia door uw departement toegespitst op afzonderlijke stoffen. De adviezen zijn opgesteld door een daartoe door mij geformeerde internationale commissie van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

De beoogde reeks van in het Engels gestelde adviezen zal losbladig worden gepubliceerd onder ons publicatienummer 2000/15OSH en, conform de aan de Gezondheidsraad voorgelegde toespitsingen van de adviesaanvraag, betrekking hebben op 168 stoffen. Het u thans aangeboden eerste pakket bestaat uit een Algemene Inleiding (publicatienummer 2000/15OSH/000) en uit de adviezen genummerd 2000/15OSH/001 tot en met 2000/15OSH/017, respectievelijk betrekking hebbend op:
cesiumhydroxide, cyclopentaan, diboraan, dimethoxymethaan, dipropylketon, fenylfosfine, germaniumtetrahydride, hexachloornaftaleen, methaanthiol, methylcyclohexanol, methylisopropylketon, mica, natriumhydroxide, octachloornaftaleen, silaan, tetrachloornaftaleen, en yttrium en yttriumverbindingen.

Bij afronding van de werkzaamheden van de hierboven bedoelde commissie ontvangt u een Nederlandstalige samenvatting van de in de gehele reeks van adviezen neergelegde bevindingen.

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Gezondheidsraad
Health Council of the Netherlands

Onderwerp : Herevaluatie uit het buitenland overgenomen grenswaarden
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De u thans aangeboden adviezen heb ik vandaag ter informatie doen toekomen aan de Minister van Volksgezondheid, Welzijn en Sport en aan de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

prof. dr JJ Sixma

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Phenylphosphine

(CAS reg no: 638-21-1)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

No. 2000/15OSH/013, The Hague, 14 December 2000

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1 Introduction

The present document contains the assessment of the health hazard of phenylphosphine by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by RN Hooftman, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research Institute, Zeist, the Netherlands).

The evaluation of the toxicity of phenylphosphine has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 24 October, 1997 (19971024/UP), 1965 to 20 October 1997 (19971020/ED), and 1967 to 28 October, 1997 (971028/ED); vol 127 iss 18), respectively. Medline was searched with the CAS Registry Number 638-21-1 and the name (mono)phenylphosphine. HSDB (no record) and RTECS, data bases available from CD-ROM, were consulted as well (NIO97). The final literature search has been carried out in October 1997.

In March 2000, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organizations: L Whitford (Health & Safety Executive, London, United Kingdom), dr P Wardenbach (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

2 Identity

name	:	(mono)phenylphosphine
synonyms	:	phosphine, phenyl-
molecular formula	:	C_6H_7P
structural formula	:	
CAS reg nr	:	638-21-1

Data from ACG91 and Ric93.

3 Physical and chemical properties

molecular weight	:	110.1
boiling point	:	160-161°C
flash point	:	73°C
solubility	:	insoluble in water soluble in alkali organic solvents (very soluble in alcohol and ether)
density	:	1.001 at 15°C
reactivity	:	spontaneously combustible in air at high concentrations
conversion factors (20°C, 101.3 kPa)		1 ppm = 4.6 mg/m^3 1 mg/m^3 = 0.22 ppm

Data from ACG91, IUC96 and Ric93.

Phenylphosphine is a clear, colourless, foul smelling liquid.

There were no data on odour threshold, but in a report on a 90-day inhalation study using rats and dogs, it was stated that a concentration of 0.6 ppm (2.8 mg/m^3) (the lowest concentration tested in this experiment) was detected by odour (duP92).

4 Uses

The compound may be used as an intermediate or as a chemical reagent (ACG91).

5 Biotransformation and kinetics

No data on biotransformation or kinetics of phenylphosphine were found.

6 Effects and mechanism of action

Human data

Potential exposure may occur in industry when phenylphosphinates, which are polyamidation catalysts and antioxidants, are heated above 200°C. Concentrations of 0.57 ppm (2.6 mg/m^3) were readily detected by an odour

panel; the odour was experienced as obnoxious. As lower concentrations were not evaluated, an odour threshold was not established (War75).

There are no human data on workers occupationally exposed to phenylphosphine.

Animal data

Adult male rats (n=6 per group) were exposed for 4 hours by inhalation. The 4-h LC_{50} was 38 ppm (175 mg/m^3) (95% C.I.: 31-47 ppm). Mild irritation such as red ears, excessive salivation, lacrimation, face-pawing, and dyspnea were observed. There were no gross or histopathological effects that could be attributed to phosphine exposure in any of the tissues (War75).

When rats (n=6) were exposed to 7.6 ppm (35 mg/m^3), 4 hours/day, 5 days/week, for 2 weeks, mild irritation similar to that in the acute study was observed together with weight loss during exposure, but the weight gain returned in the subsequent 14-day recovery period. A transient dermatitis around mouth and feet appeared after the last exposure. Increased haematopoiesis in the spleen occurred, not returning to normal during the recovery period (War75). Furthermore, oligospermia was reported to have occurred in this study (duP92).

In a 90-day inhalation study, male and female rats (Charles-River CD: n=20 per sex per group) and male dogs (beagle; n=4 per group) were exposed to phenylphosphine for 6 hours/day, 5 days/week, to approximate average concentrations of 0, 0.6, or 2.2 ppm (0, 2.8, and 10 mg/m^3, respectively). Thirty rats (n=5 per sex per group) and 6 dogs (n=2 per group) at a time were sacrificed after 30 and 90 days and after a 28-day recovery period, while the remaining rats were killed after a 65-day recovery period. Parameters studied included clinical observations (schedule not reported) and clinical chemistry analysis (rats: once prior to the start, 4 times during the test, twice during the recovery period; dogs: twice, 4 times, and once, resp; parameters: erythrocyte counts, haemoglobin concentration, haematocrit, total leukocyte count), and all animals sacrificed were examined grossly and histologically. Treatment did not result in mortality in any of the rat and dog exposure groups. In rats of the low exposure group (2.8 mg/m^3), hypersensitivity to sound and touch and mild hyperaemia were observed from the first month onwards both during and after the daily exposures (no data on incidence or severity were given). At the end of the exposure period, mild dermatitis and decreased body weight (concluded from a graph; no data or statistical analysis presented) occurred. Only slight

changes in erythrocyte counts, haemoglobin concentrations, and haematocrit were observed. Apart from a mild increase in red blood cell formation in the spleen in 5 out of 5 (5/5) female and 2/5 male rats and an increased spleen weight at the 30-day time point*, no changes were found upon any of the postmortem examinations. The committee noticed that high dose group severe testicular damage similar to that observed in the group 1/5 animals at day 90 showed; this was not seen in the animals examined after the recovery periods. Exposure to 2.2 ppm (10 mg/m^3) induced similar effects, but to a more severe extent (no details presented). In addition, dermatitis around eyes, mouth, and feet were seen. At the end of exposure, there were hair loss, red swollen areas around the extremities, and, in male animals, a marked decreased body weight (see remark 0.6 ppm group). Throughout the experiment, decreased erythrocyte counts, haemoglobin concentrations, and haematocrit and increased leukocyte counts were seen, reaching statistical significance in the male animals for all measurements at every examination. Postmortem examinations at the 30-day time point showed a greater increase in red blood cell formation in all male and female animals and increased spleen weights. Severe testicular degeneration, characterized by the loss of germinal cells, severe stromal oedema, proliferation of interstitial cells, and aspermia in semiferous tubules as well as the epididymis, and mild haemolytic anaemia were found in males sacrificed at the end of the exposure period. Average testis weights were more that 50% lower than those of control animals (1.62 g vs 3.46 g). Most of the changes returned to normal following the 28- or 65-day recovery period, but the testicular degeneration was still present after the 65-day recovery period. Finally, various degrees of chronic murine pneumonia and tracheitis were found in the test groups at different sacrifices. Since this was found to a similar incidence and severity in the control animals as well, they could not be attributed to exposure to phenylphosphine. In dogs, exposure did not affect body weight (gain). In the animals of the low exposure group (2.8 mg/m^3), intermittent loss of appetite (in 1/4), nausea (in 1/4), diarrhoea (in 4/4 at the first time point only), and lacrimation (no incidences given) were observed during but not after the daily exposure periods. There were no effects on the clinical chemistry parameters. Apart from a moderate haemopoietic activity in the bone marrow at the 90-day sacrifice, no changes were seen in any of the postmortem examinations. Exposure to 2.2 ppm (10 mg/m^3) induced similar signs, but to a more severe extent, as well as hind leg tremors (in 2/4) and intermittent increased water consumption (in 4/4). Erythrocyte counts, haemoglobin concentrations, and

* At this time point, only the spleen was examined in animals of the low exposure group.

haematocrit were decreased at every time point during the exposure period. Upon postmortem examinations, a mild haemolytic anaemia and testicular degeneration were observed. The testicular degeneration was mild compared to that seen in rats. It was stated that these testicular lesions were reversible. However, the committee could not verify this from the copy of the report that was made available (duP92).

No no observed adverse effect levels (NOAELs) could be derived from this study, since exposure to 0.6 ppm (2.8 mg/m^3), the lowest level tested, for 6 hours/day, 5 days/week, for 90 days, induced dermatitis and some slight clinical signs in rats (observed both during and after the daily exposures) and some slight clinical signs in dogs (during exposure). Furthermore, the severe testicular damage observed in one out of 5 male rats exposed to 2.8 mg/m^3 and sacrificed immediately after the end of exposure was considered to be treatment related as well.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for phenylphosphine in the Netherlands is 0.05 ppm (0.25 mg/m^3), as a ceiling limit.

Existing occupational limits for phenylphosphine in some European countries and the USA are summarized in the annex.

8 Assessment of health hazard

No data on occupationally exposed workers, biotransformation, kinetics, mutagenicity, genotoxicity or carcinogenicity of phenylphosphine have been found.

From the 4-h LC_{50} of 38 ppm (175 mg/m^3) in rats, phenylphosphine should be considered as very toxic by inhalation (War75).

From repeated inhalation exposure experiments, it can be seen that phenylphosphine induced haematological effects and effects on the testes in both rats and dogs, and that rats were the more sensitive species (duP92). In the subchronic inhalation study in rats, exposure to 2.2 ppm (10 mg/m^3), 6 hours/day, 5 days/week, for 90 days, caused severe testicular damage, which was persistent even after a 65-day recovery period, and a mild haemolytic anaemia. The haematological effects were not seen at 0.6 ppm (2.8 mg/m^3), the

lowest level tested, but dermatitis, some slight clinical signs and severe testicular damage (in one out of 5 animals sacrificed at day 90) were found.

The lowest observed adverse effect level (LOAEL) of 2.8 mg/m^3 in the aforementioned subchronic inhalation study in rats is taken as a starting point in deriving a health-based occupational exposure limit (HBROEL). For the assessment of a HBROEL, the following considerations were taken into account: intra- and interspecies variation, differences between experimental conditions and the exposure pattern of the worker, and the absence of an NOAEL. The committee considered an overall assessment factor of 54 to be appropriate for the extrapolation from the subchronic LOAEL in rats to a working lifetime exposed worker. Applying this factor and assuming that the dose inhaled by rats is equivalent to the dose inhaled by humans, a preferred value of 0.05 mg/m^3 (0.01 ppm) is recommended as a HBROEL for phenylphosphine. This level is considered to prevent workers from haematological effects and effects on the male reproductive system.

The committee recommends a health-based occupational exposure limit for phenylphosphine of 0.05 mg/m^3 (0.01 ppm), as an 8 h time weighted average (TWA).

References

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ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). 2000 TLVs® and BEIs®. Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH, 2000.

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DFG99 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1999. Maximale Arbeitsplatzkonzentrationen und biologischeArbeitsstofftoleranzwerte. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1999; Mitteilung 35.

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HSE99 Health and Safety Executive (HSE). EH40/99 Occupational Exposure limits 1999 Sudbury (Suffolk), England: HSE Books, 1999

NBO96 National Board of Occupational Safety and Health. Occupational exposure limit values. Solna, Sweden: NBOSH, 1996; Ordinance AFS1996/2.

NIO97 US National Institute of Occupational Safety and Health (NIOSH). Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM], issue October 1997. SilverPlatter International, 1997 (last update phenylphosphine file: October 1997).

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SZW00 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). De nationale MAC-lijst 2000 The Hague, The Netherlands: Servicecentrum Sdu Uitgevers, 2000.

TRG00 TRGS 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe; B Arb Bl 2000; 2.

War75 Waritz RS, Brown RM. Acute and subacute inhalation toxicities of phosphine, phenylphosphine and triphenylphosphine. Am Ind Hyg Assoc J 1975; 6: 452-8.

Annex

Occupational exposure standards for phenylphosphine in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
The Netherlands						
-Ministry	0.05	0.25	ceiling	administrative		SZW00
Germany						
-AGS	-	0.25	ceiling			TRG00
-DFG MAK-Kom.	-	-				DFG99
Great-Britain						
-HSE	-	-				HSE99
Sweden	-	-				NBO96
Denmark	0.05	0.25	ceiling			Arb96
USA						
-ACGIH	0.05	0.23	ceiling	TLV		ACG00
-OSHA	-	-	ceiling	PEL		
-NIOSH	0.05	0.25	ceiling	REL		
European Union						
-SCOEL	-	-				

[a] S = skin notation; this means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.